Clinical Needs for Biomedical Imaging

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MedscapeWire

MRI and CT Ranked the Top Medical Innovations by Physicians

October 11, 2001

New York - Physicians surveyed about the most important innovations of the last 25 years ranked interventions for cardiovascular disease and high-tech scanning devices such as magnetic resonance imaging (MRI) and computed tomagraphy (CT) among the most important. They ranked bone marrow transplantation and the erectile dysfunction drug sildenafil among the least important innovations.

The ranking of the 30 medical innovations in the study are as follows:

1. MRI and CT
2. ACE inhibitors
3. Balloon angioplasty
4. Statins
5. Mammography
6. Coronary artery bypass graft
7. Proton pump inhibitors and H2 blockers
8. Selective serotonin reuptake inhibitors (SSRIs) and new non-SSRI antidepressants
9. Cataract extraction and lens implant
10. Hip and knee replacement
11. Ultrasonography and echocardiography
12. Gastrointestinal endoscopy
13. Inhaled steroids for asthma
14. Laparoscopic surgery
15. Nonsteroidal anti-inflammatory drugs and COX-2 inhibitors
16. Cardiac enzymes
17. Fluoroquinolones
18. New hypoglycemic agents
19. HIV testing and treatment
20. Tamoxifen
21. Prostate-specific antigen testing
22. Long-acting and local opioid anesthetics
23. *Helicobacter pylori* testing and treatment
24. Bone densitometry
25. Third-generation cephalosporins
26. Calcium channel blockers
27. Intravenous conscious sedation
28. Sildenafil (Viagra)
29. Nonsedating antihistamines
30. Bone marrow transplant

Fuchs and Sox, Health Affairs 2001 20(5):30-43

Global Burden of Disease

1990 - Developed Regions

thousands of disability-adjusted life years lost

1.	Ischemic heart disease	15,950	9.9%
2.	Unipolar major depression	9,780	6.1
3.	Cerebrovascular disease	9,425	5.9
4.	Road traffic accidents	7,064	4.4
5.	Alcohol use	6,447	4.0
6.	Osteoarthritis	4,681	2.9
7.	Respiratory cancers	4,587	2.9
8.	Dementia	3,816	2.4
9.	Self-inflicted injuries	3,768	2.3
10.	Congenital anomalies	3,480	2.2
		~65M	

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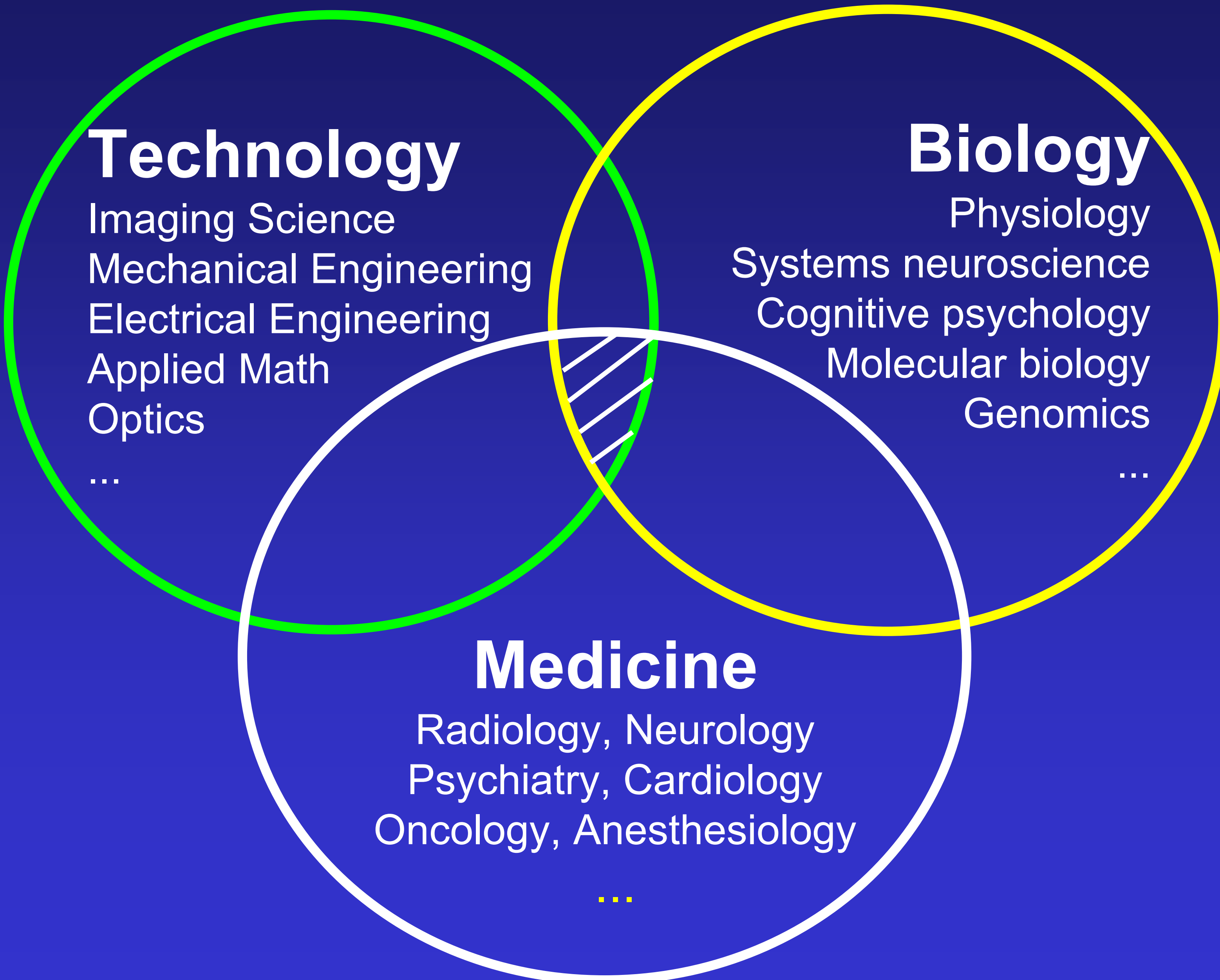
Global Burden of Disease

1990 - Established Market Economies

Percentage distribution of disability-adjusted life years

• Neuro-psychiatric conditions	25.1%
• Cardiovascular diseases	18.6
• Malignant neoplasms	15.0
• Injuries	11.9
• Communicable, maternal, perinatal, and nutritional conditions	7.1

NIBIB Community



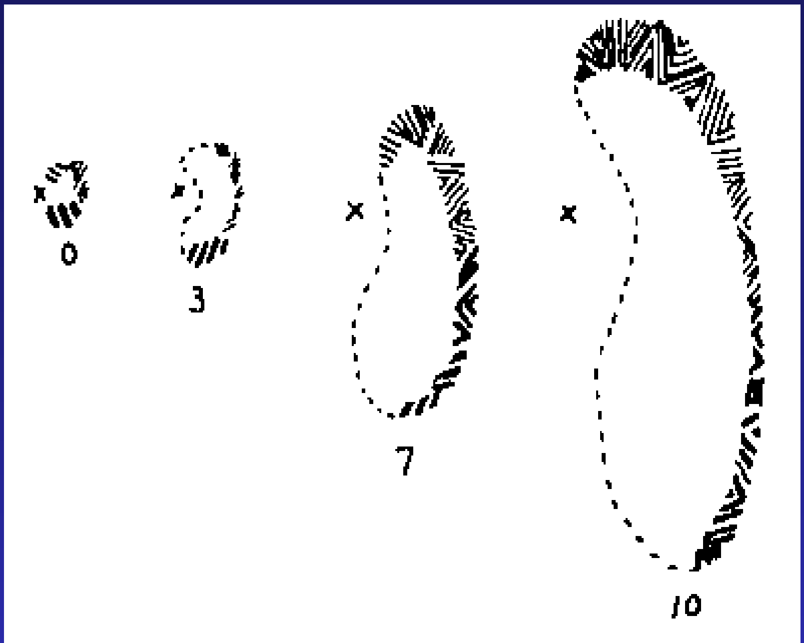
Imaging for Clinical Research

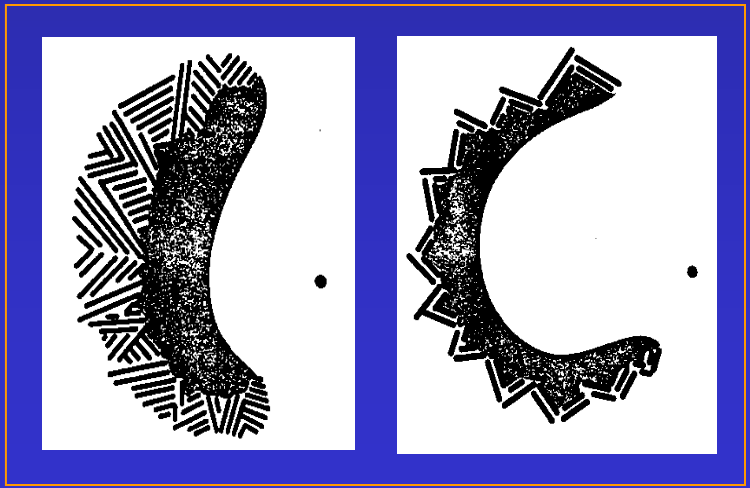
An example: Migraine

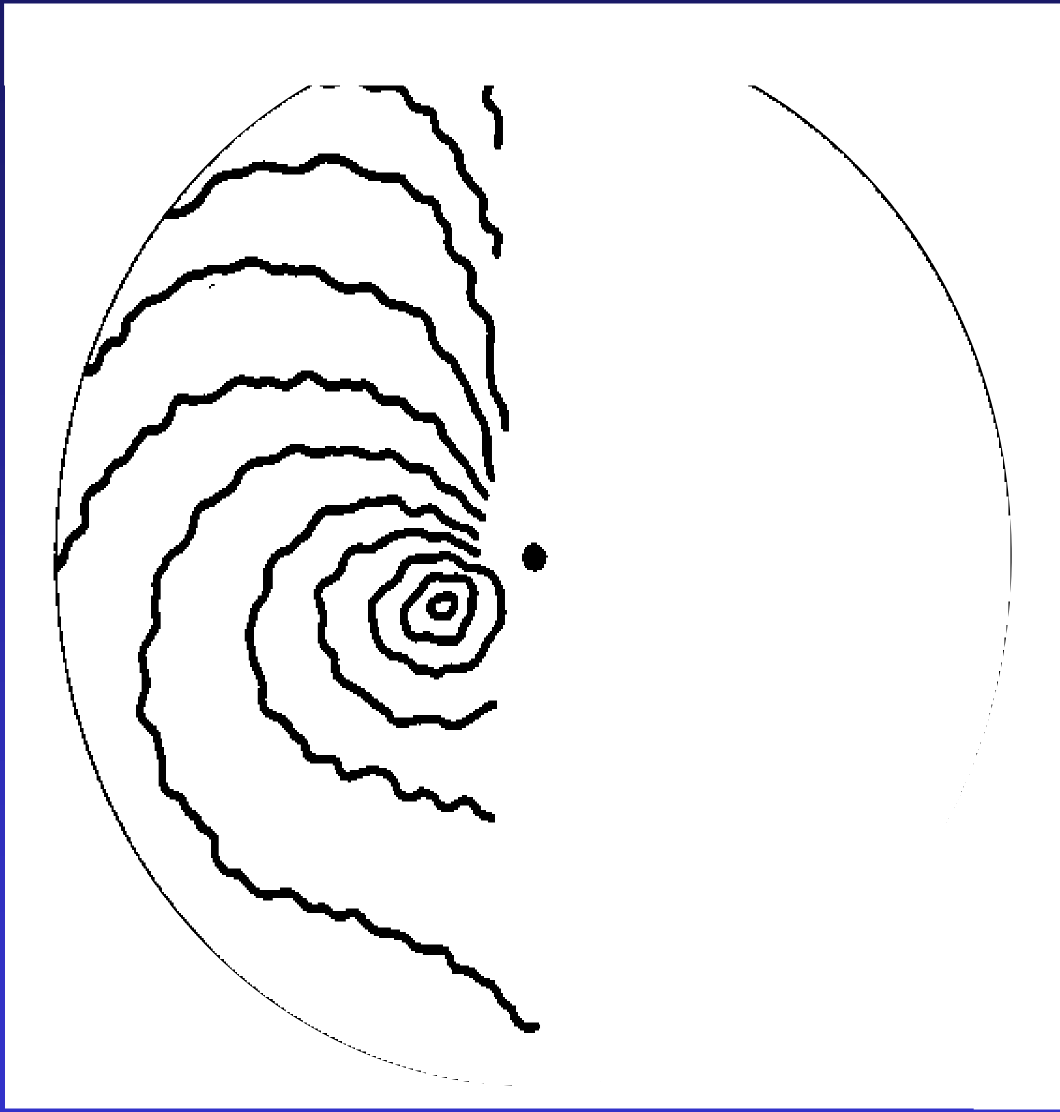
(with thanks to Nouchine Hadijkani and Mike Moskowitz)

- Very common disorder (up to 18% of the population)
- No generally efficient treatment
- 20% of people with migraine have auras preceding the headache
- *Understanding what happens before a headache may help understand disease mechanisms and design better treatments*

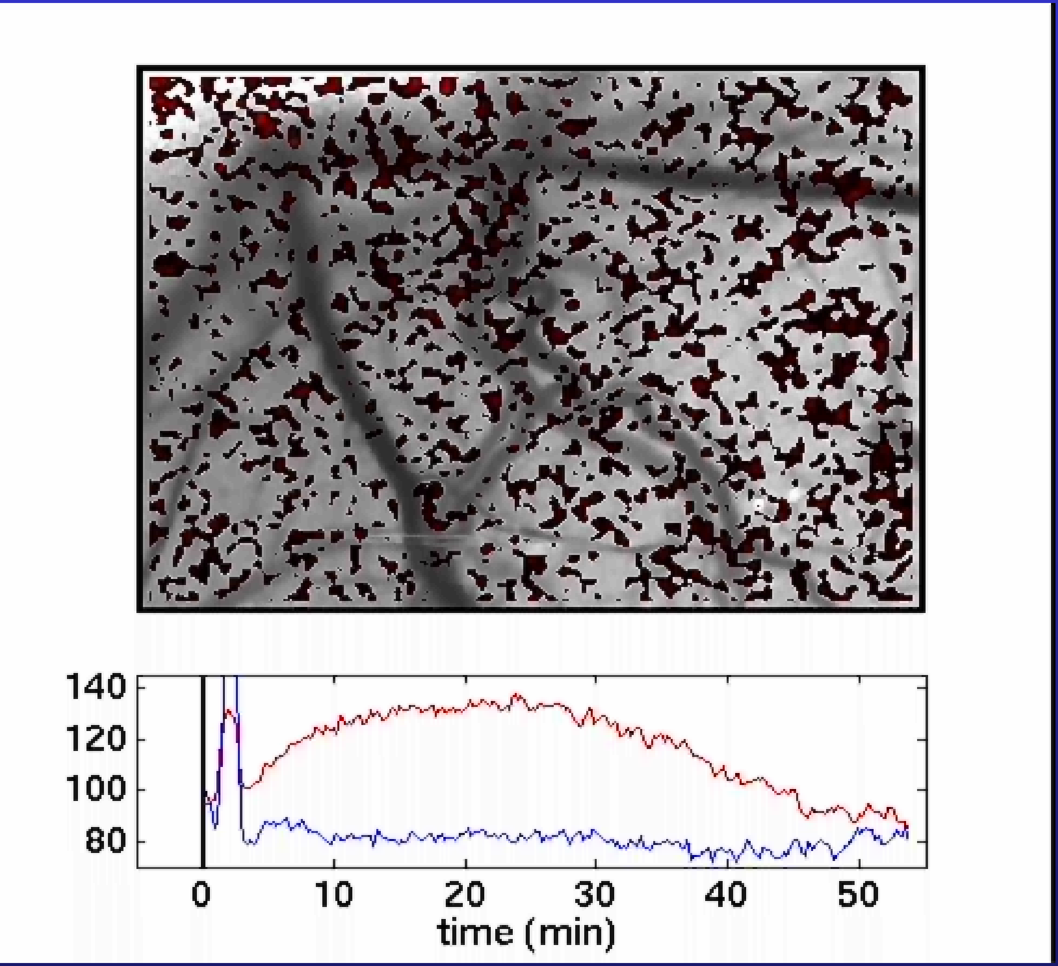
Typical auras from the literature





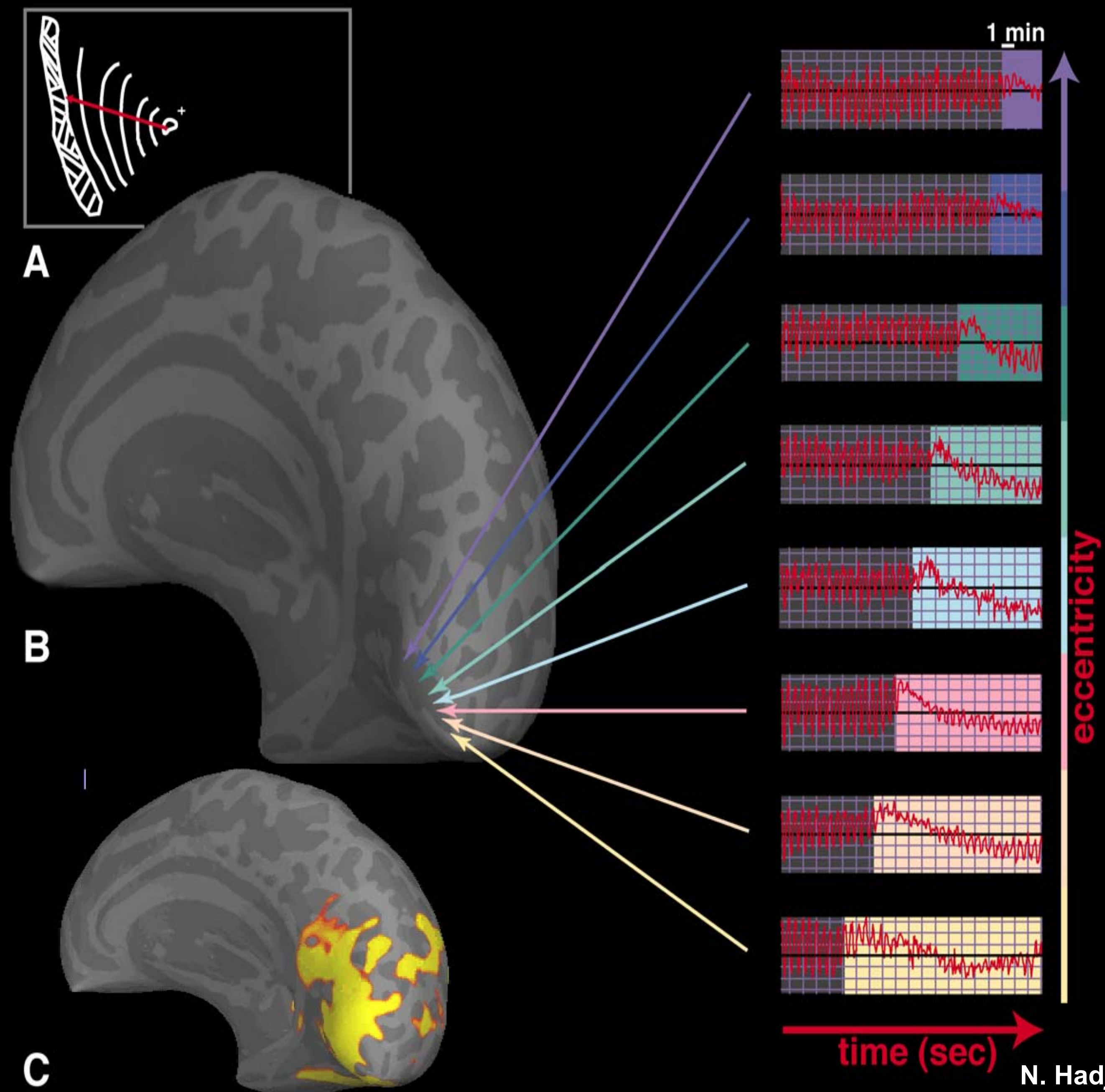


Cortical Spreading Depression



Is Migraine a primary vascular, or neuronal, event?

Timing of the signal change along V1, with increasing eccentricity



N. Hadjikhani MGH-NMR Cent

Migraine Aura vs CSD

- Migraine visual aura
  - hyperemia 3.3±1.9 min
  - hypoperfusion- 2 hours
  - cortical suppression of activation- 3.5±1.1mm/min
  - recovery 80% amplitude in 15min
- CSD
  - hyperemia 3-4.5 min
  - hypoperfusion- 1-2h
  - 2-5 mm/min
  - evoked activation -15-30min

***These data support the neuronal, not vascular, theory of migraine*.**

Implications

CSD implicated in migraine aura

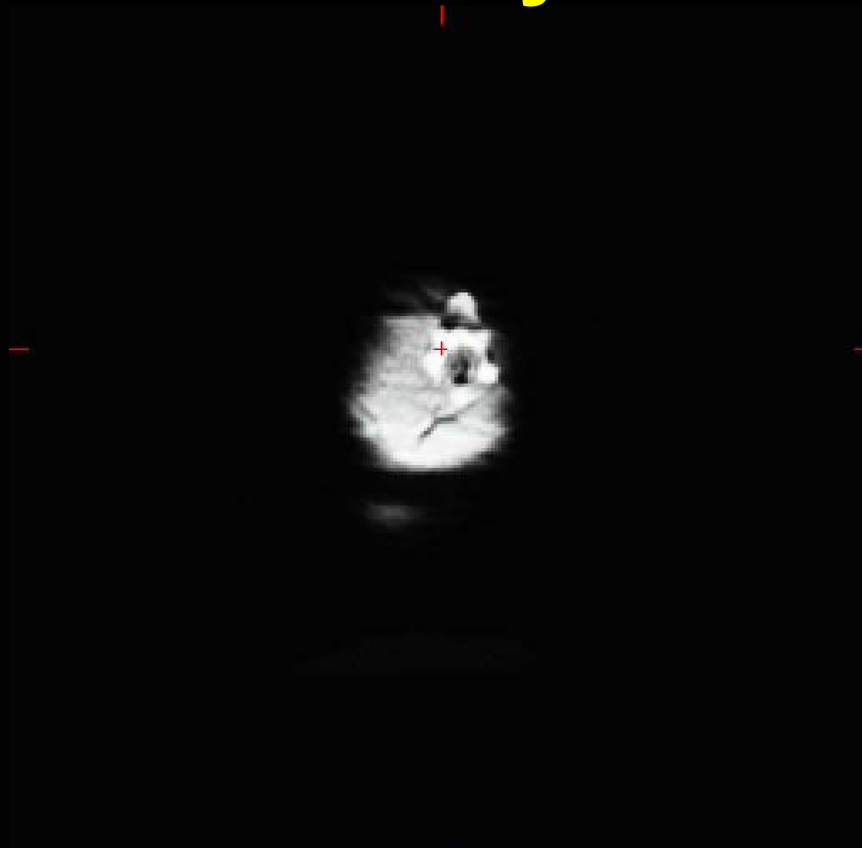
- Intense brain activity like CSD =>
- Release of ions and neurotransmitters from cortex in proximity to meninges =>
- Triggers trigeminovascular axons within its connective tissue capsule (meninges) =>
- Disruption of cellular compartments, altered basement membrane properties, and cross-talk between brain and meninges =>
- Vascular dilatation and PAIN

Courtesy Andy Dunn and David Boas

New Technologies
Opportunities to Expand our Model

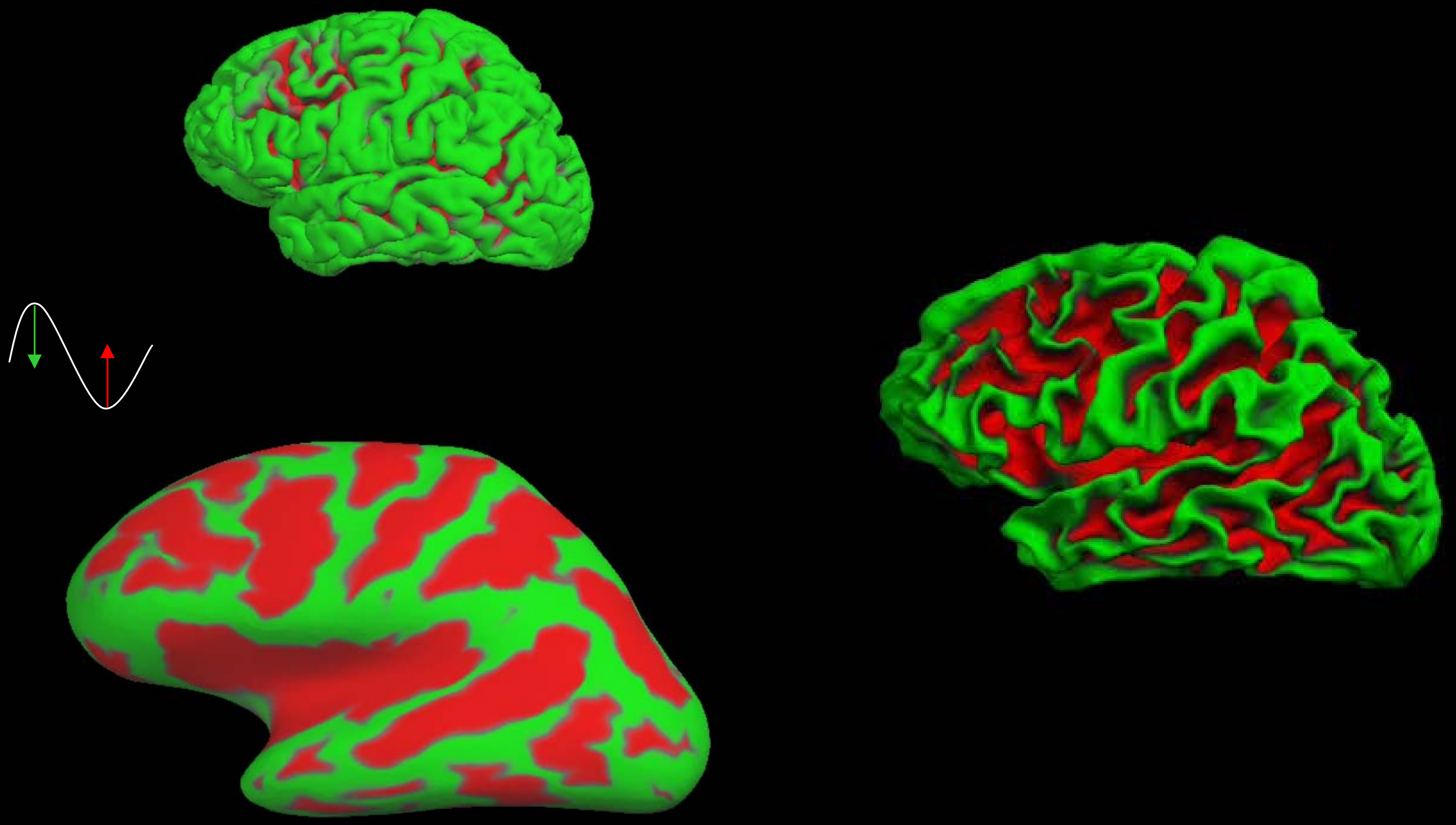
- Quantitative/high resolution morphometric imaging (MRI,CT)
- Hemodynamic imaging (MRI, CT, PET, Optical)
- Connectivity mapping (diffusion MRI)
- Biochemical imaging (MRS, PET, optical)
- Molecular imaging (PET, optical, ?MRI)
- “Activation” (functional) imaging (fMRI, PET, optical, EEG/MEG)

Segmentation with Gibbs Priors: Fly Through

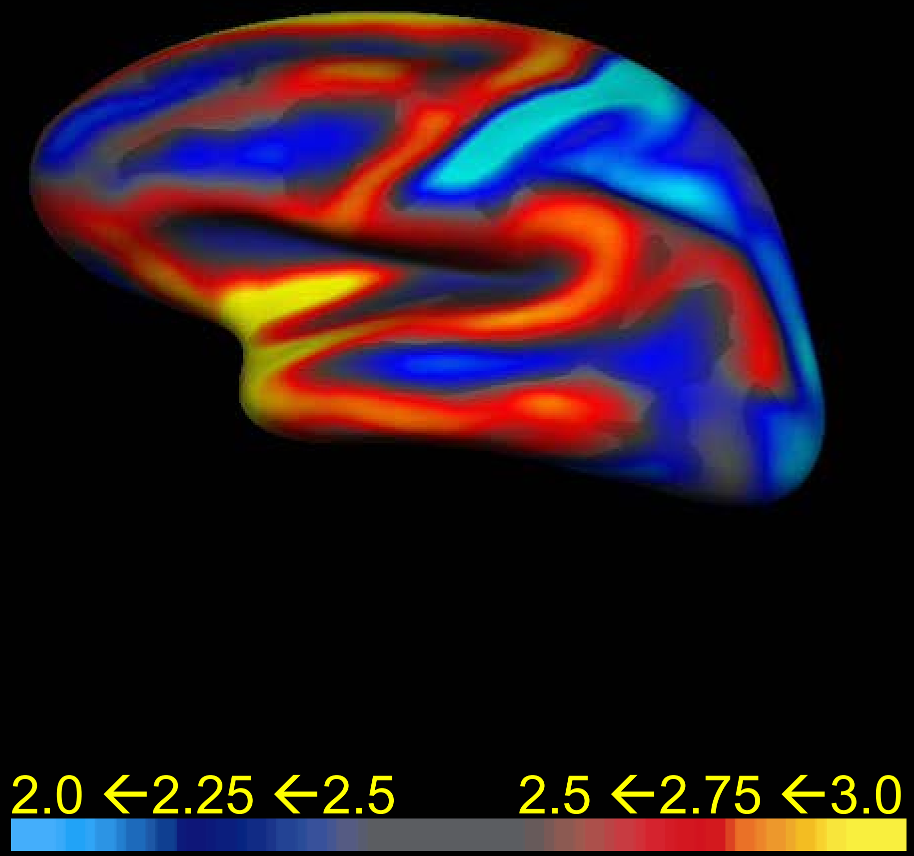


Cerebellar cortex	LH cerebral WM	Cerebral cortex	Amygdala
Cerebellar WM	Hippocampus	Misc.	
4th ventricle	LH pallidum	Lateral ventricle	
RH cerebral WM	Thalamus	Caudate	

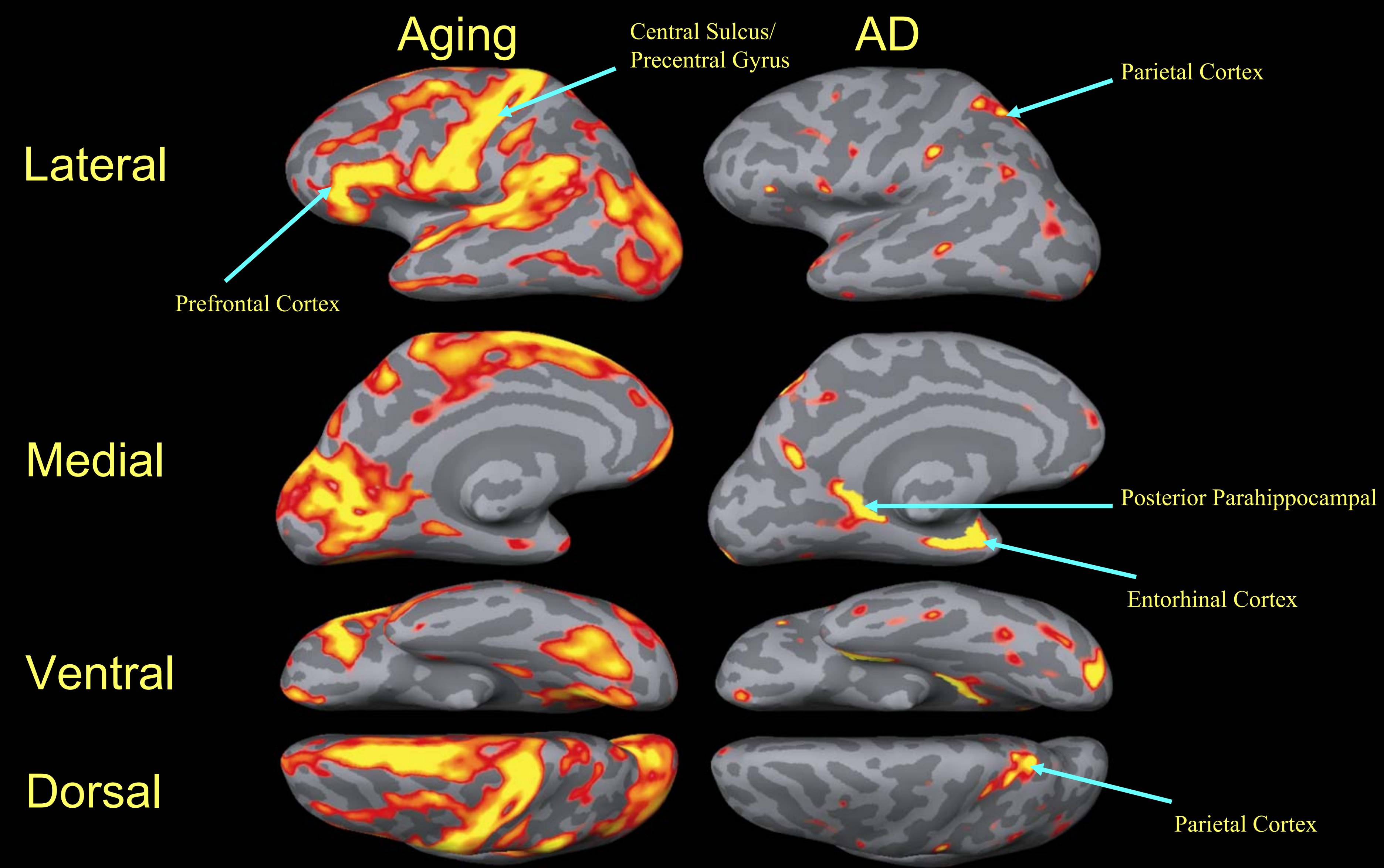
Surface Inflation



The Movie of Cortical Thinning with Aging

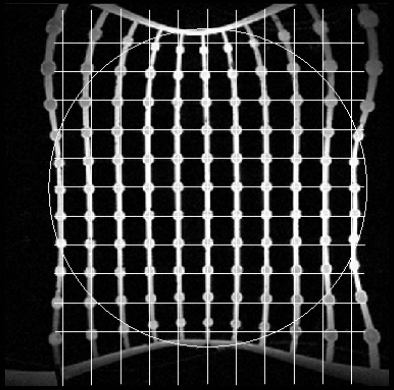


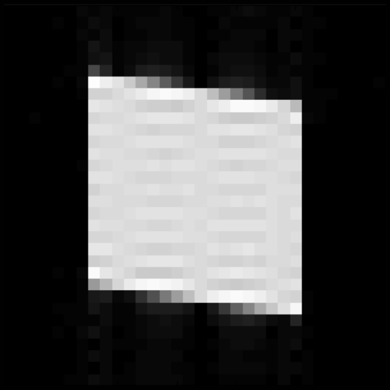
Selective Regional Thinning in AD

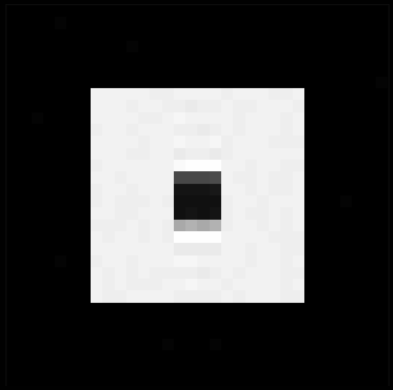


Towards Site-Independent Analysis: NIH-sponsored Biomedical Imaging Research Network ("BIRN")

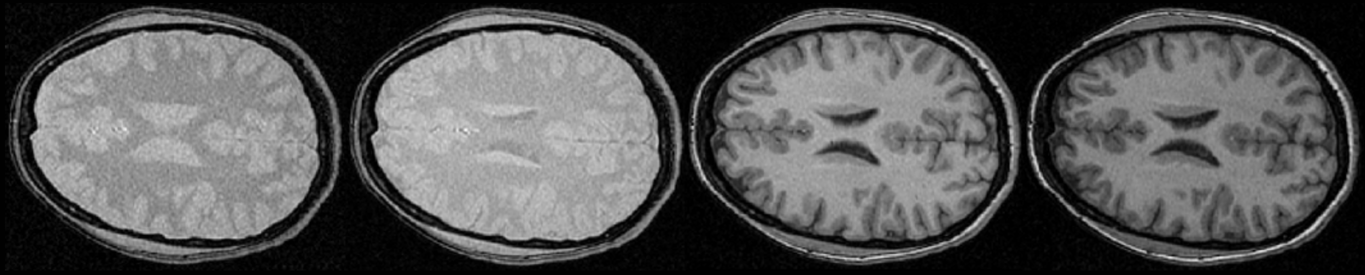
Scanner/Protocol/Subject-Specific Spatial Distortions







Scanner/Protocol-Specific Tissue Contrast



Goal: Develop optimized imaging protocols and post-processing algorithms that allow for precise, quantitative analysis and comparison of data across sites, studies and time.

Overall Goal:
Brain Morphology BIRN

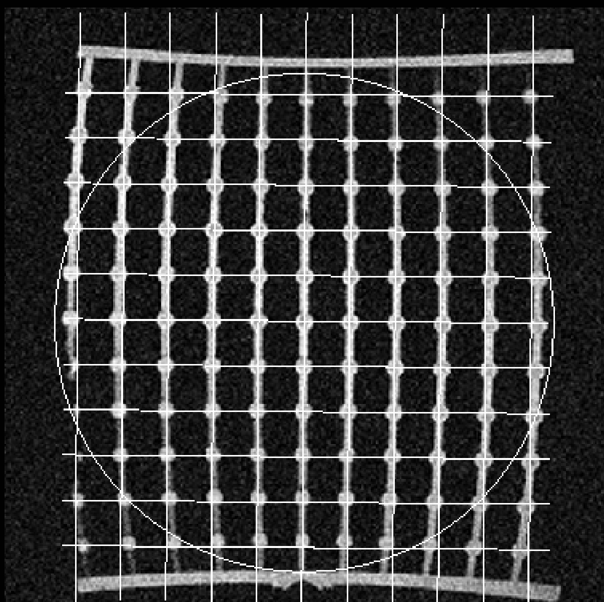
To develop the capabilities to analyze, as a single dataset, data acquired across multiple sites, on different platforms, using tools developed by multiple sites.

mBIRN Site Contributions- Integration of:

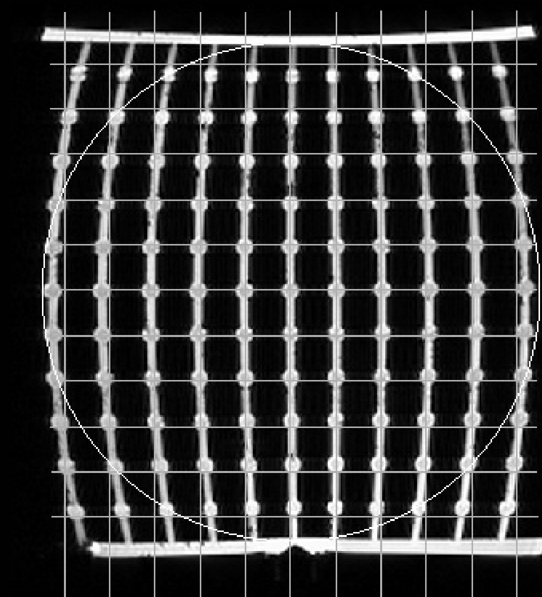
- UCSD – Storage Resource Broker Architecture & Database tools
- UCLA – Data Pipeline
- MGH – Automated Segmentation tools & Spatial Correction tools
- BWH – Visualization tools
- Duke – Morphometry tools and clinical data
- Hopkins – Shape analysis tools

- All – Patient and control Data

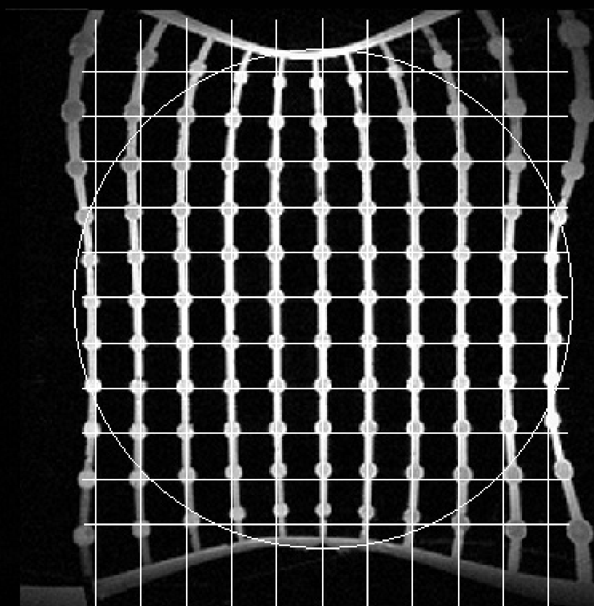
MRI Distortions due to Gradient Non-Linearities



Siemens Whole-Body
Symphony/Sonata
Max displ. 2.5/3.2mm



GE Whole-Body
CRM NVi/CVi
Max displ. 4.2/8.6mm



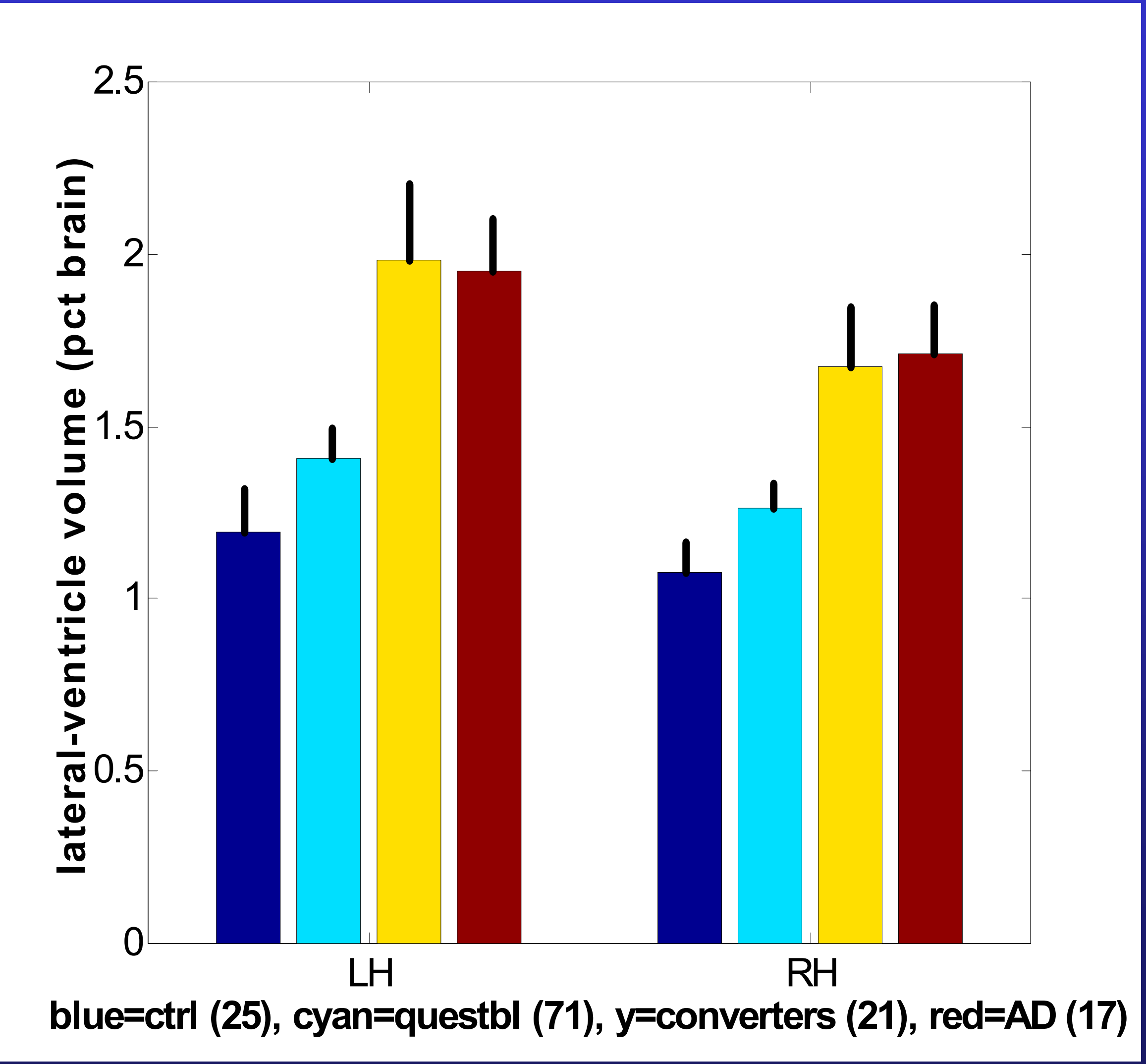
Siemens Head-Only
Allegra/AC-44
Max displ. 5.7/20.2mm

Symptom and Diagnosis Related Clinical Specific Aims.

Hypothesis: Decreased amygdala volume and thinning of the DLPFC will predict the severity of depression within each diagnostic category (unipolar depression, MCI and mild AD).

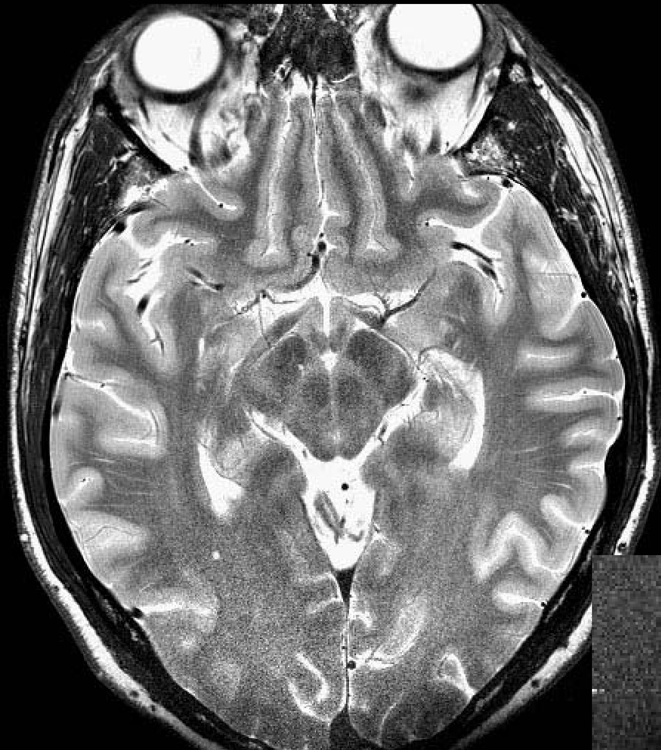
Hypothesis: Non-demented ApoE 4 homozygotes will have greater asymmetries of hippocampal volume and of the cortical ribbon in the inferior parietal lobe than age- and sex-matched controls.

Results: Ventricular Volume



Data courtesy of Drs Marilyn Albert and Ron Killiany

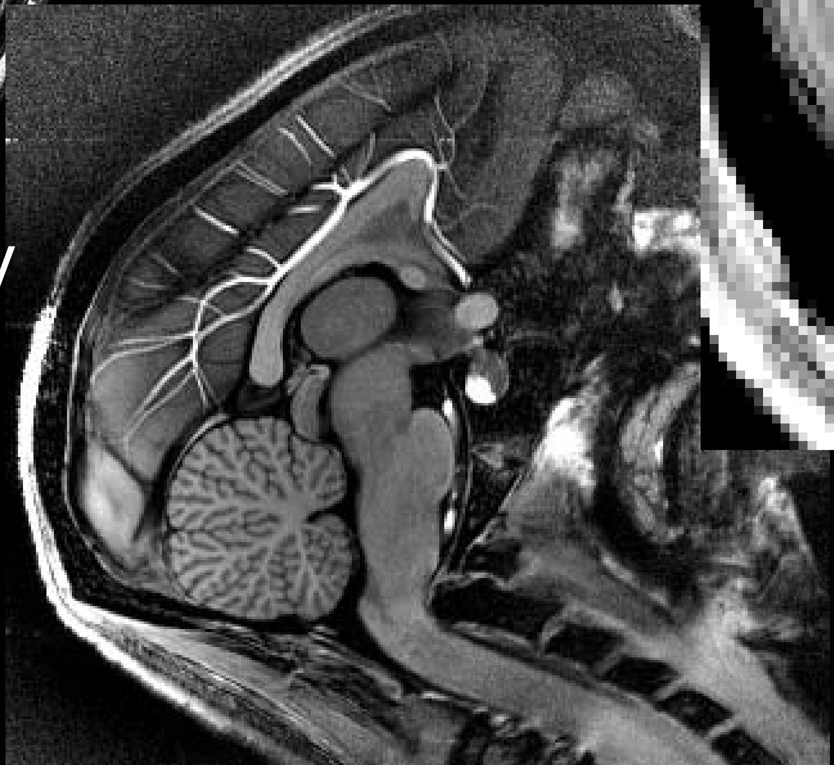
Technology is a Moving Target



3T Phased Array
350um

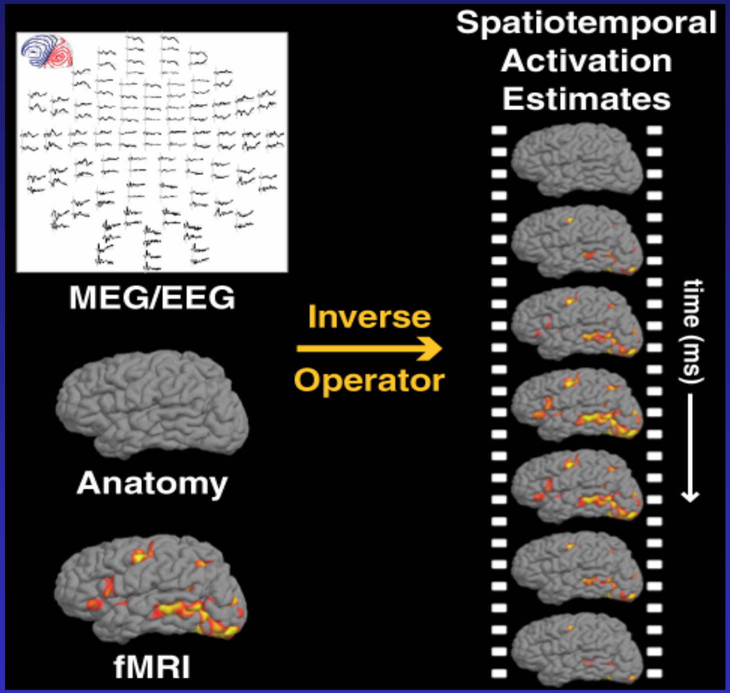
Cortical Layers at
7T – 250um

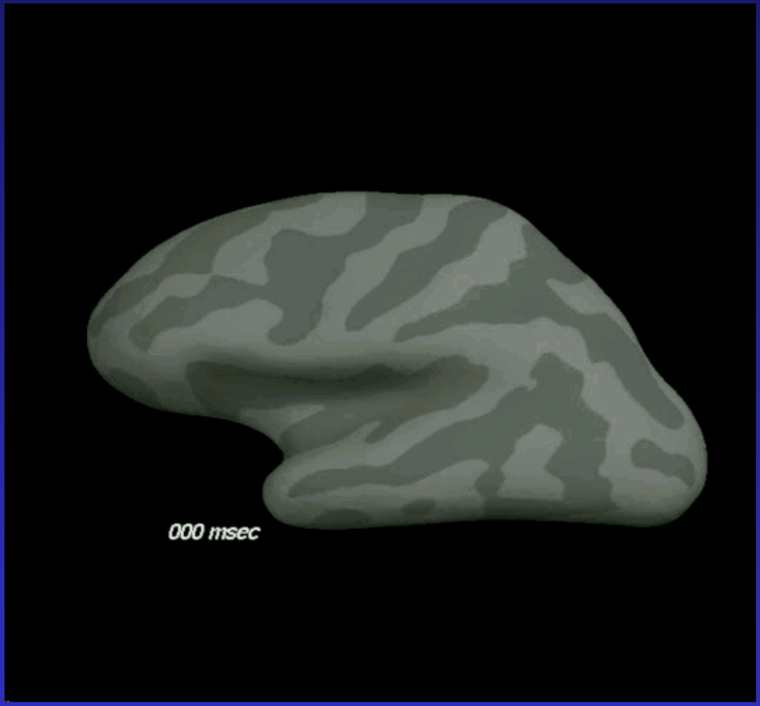
7T Primate



A Few Modest Examples of our Opportunities

Develop a Systems Biology of Human Cortex

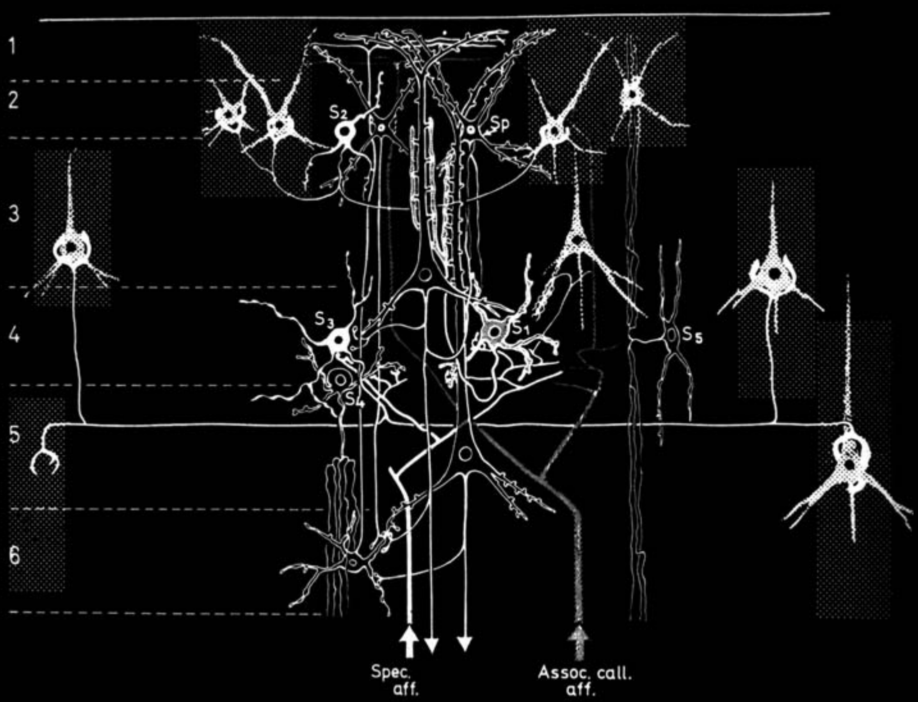


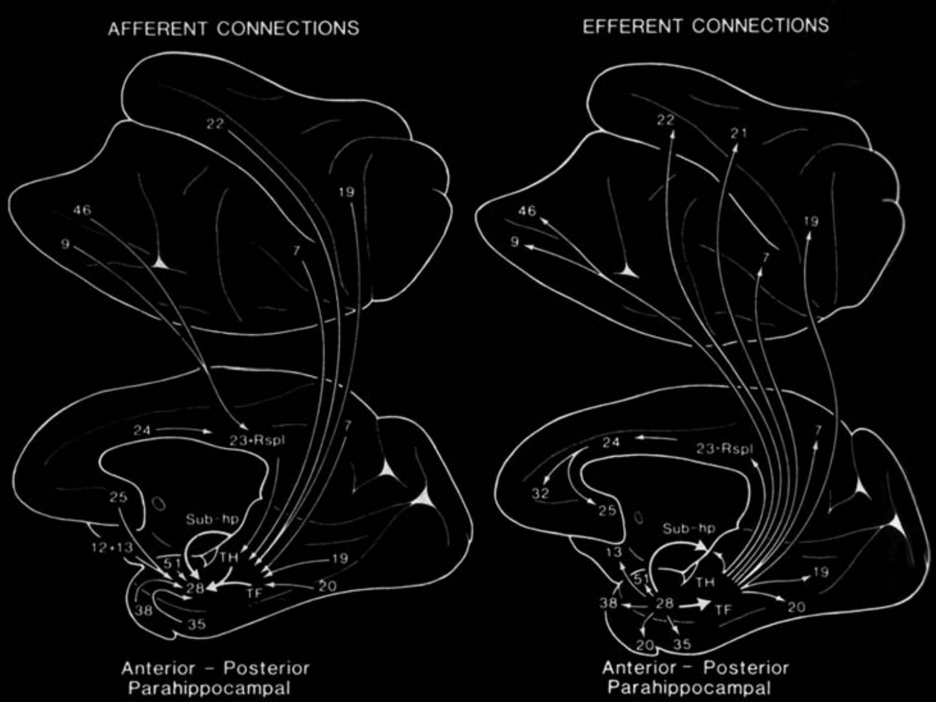


Reading a word

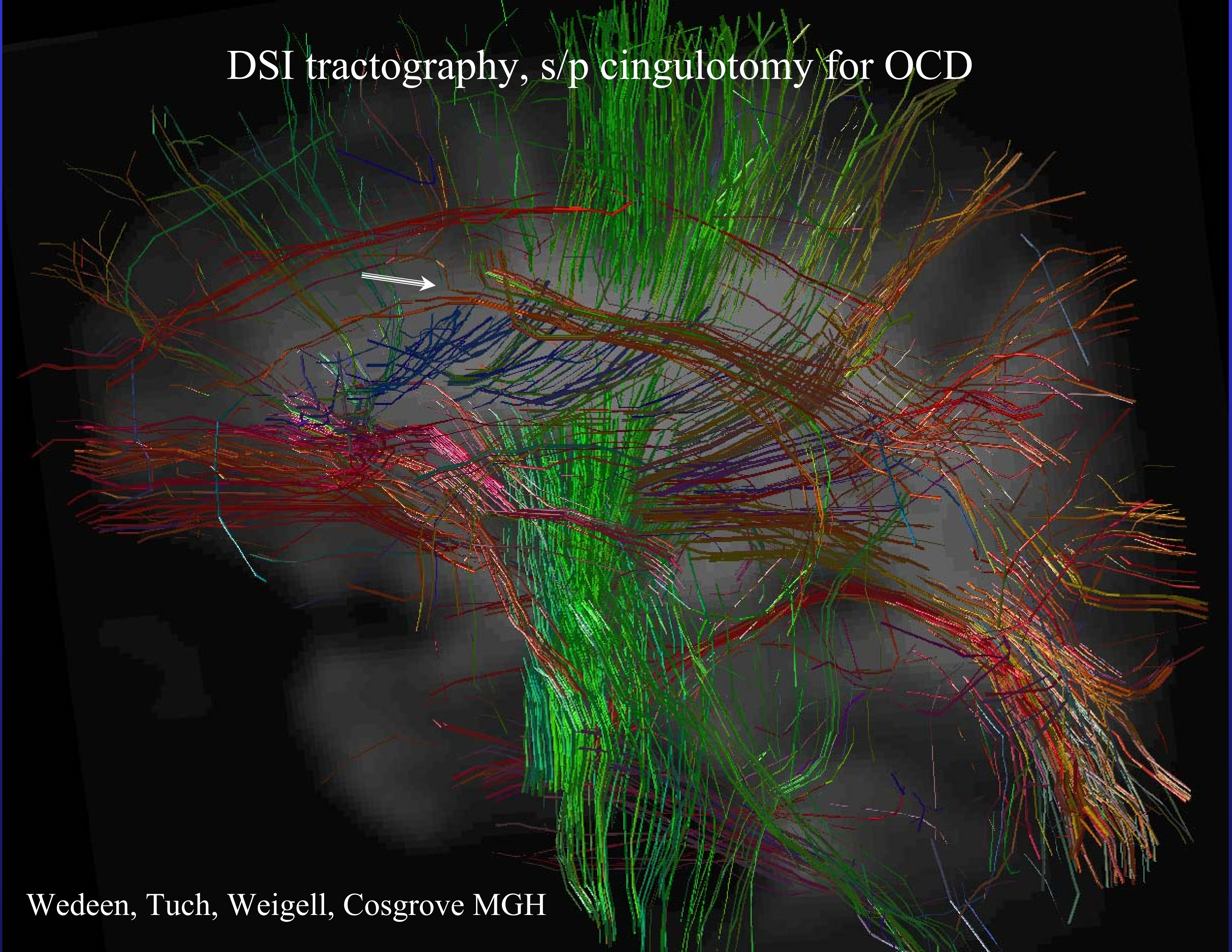
- We can make movies of the brain in action, now we want to know what those movies mean
- Integrate Advanced Neuroimaging with cortical biology, using Computational and Biophysical models, to develop a comprehensive Systems Neurobiology of cortical function

Cortical Circuitry and Connections



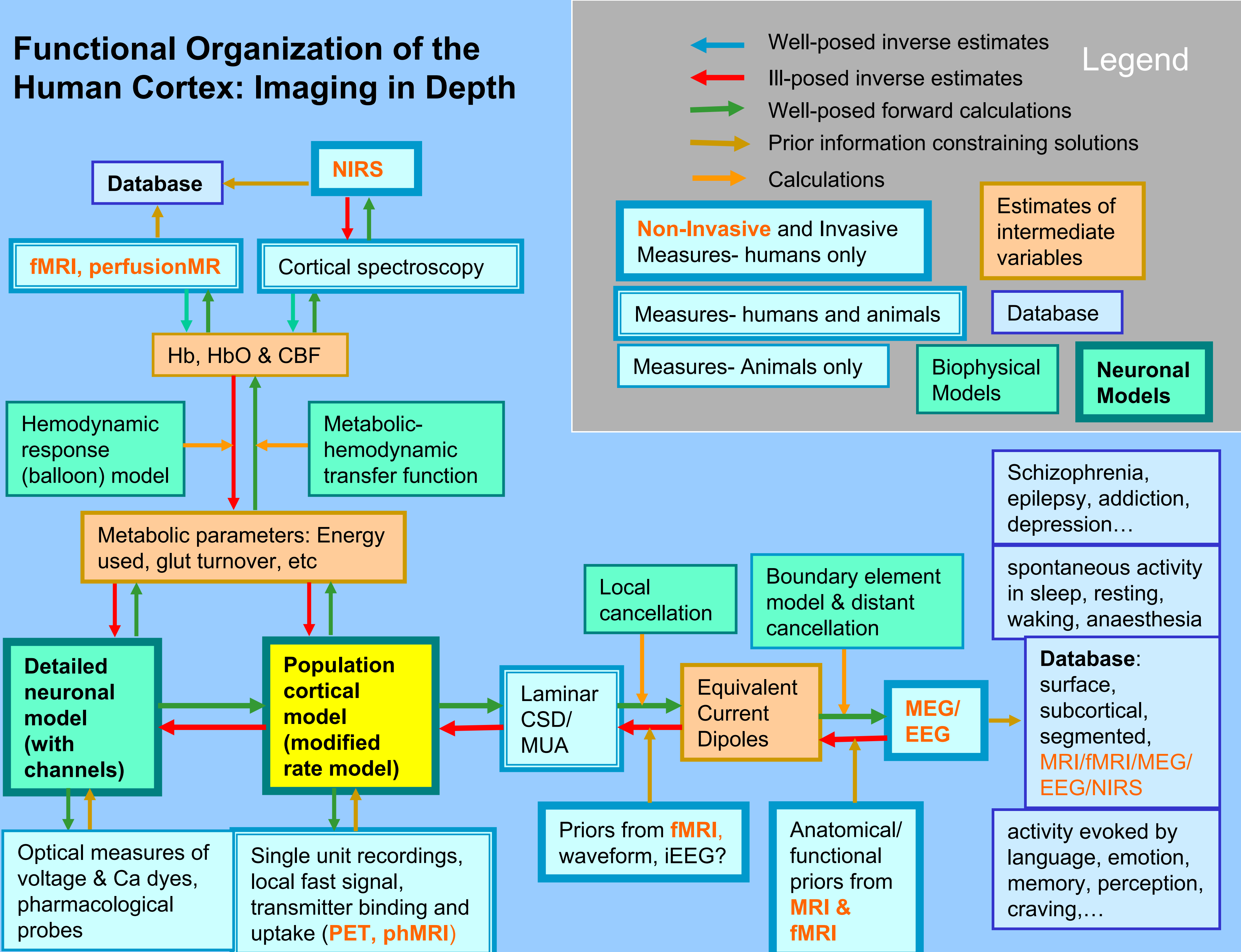


DSI tractography, s/p cingulotomy for OCD

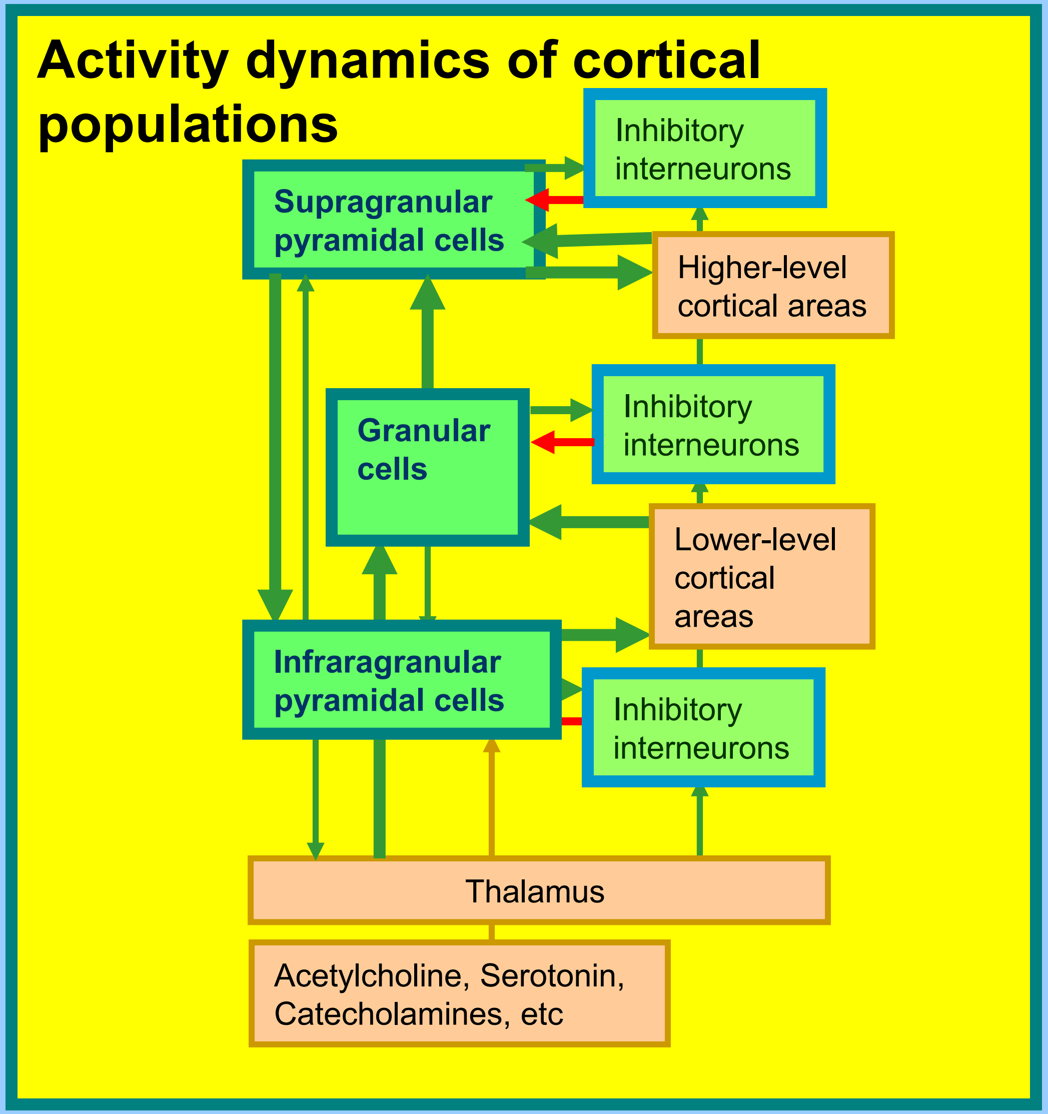


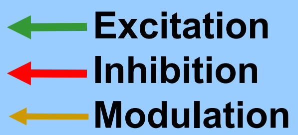
Wedeen, Tuch, Weigell, Cosgrove MGH

Functional Organization of the Human Cortex: Imaging in Depth



Population Cortical Model: The mechanics of thought

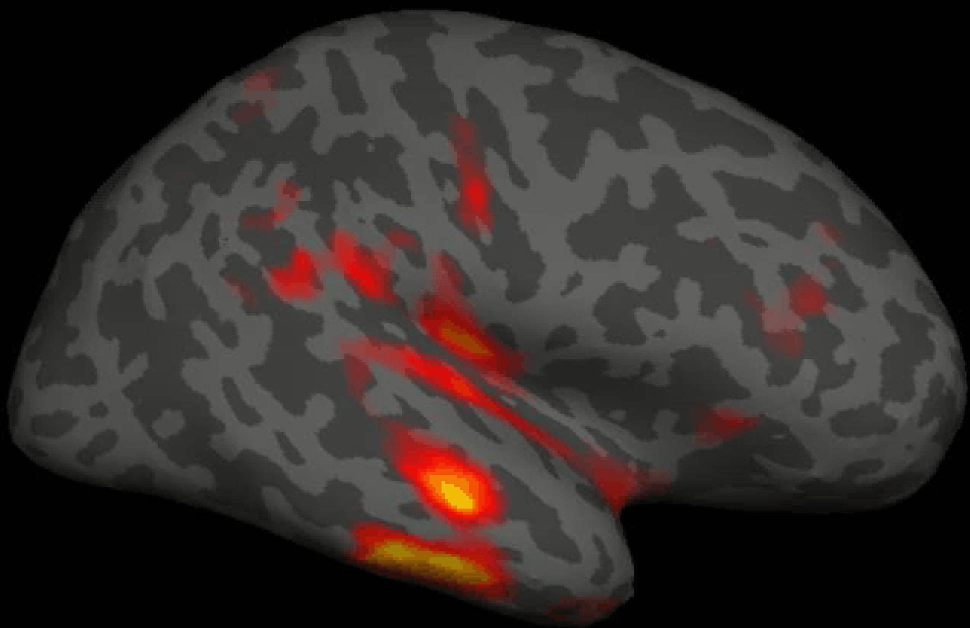


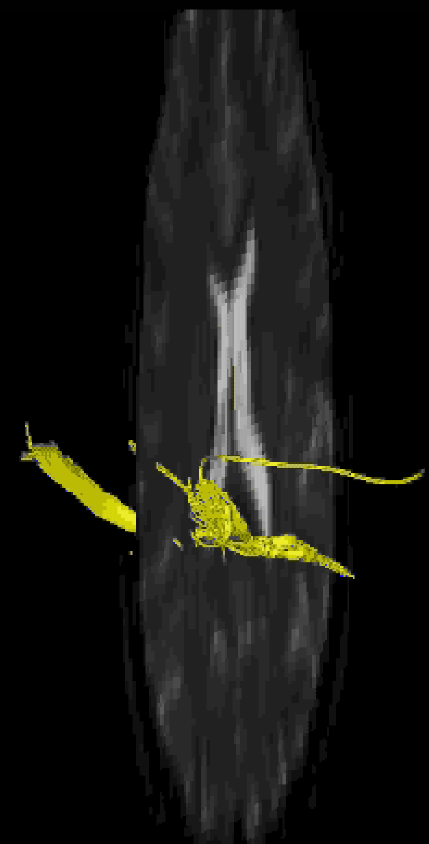


An active functional mathematical model defining communication between cortical neurons.

The ultimate goal of this project is to make this model and develop methods for defining its critical parameters from non-invasive measures.

Intraictal spike:
Temporal to frontal propagation

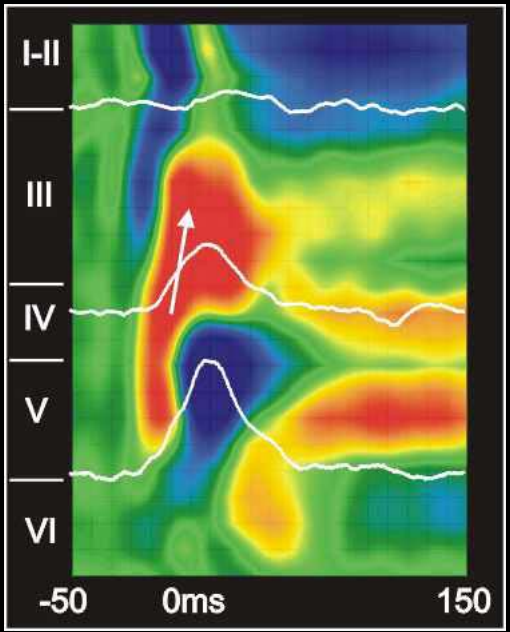


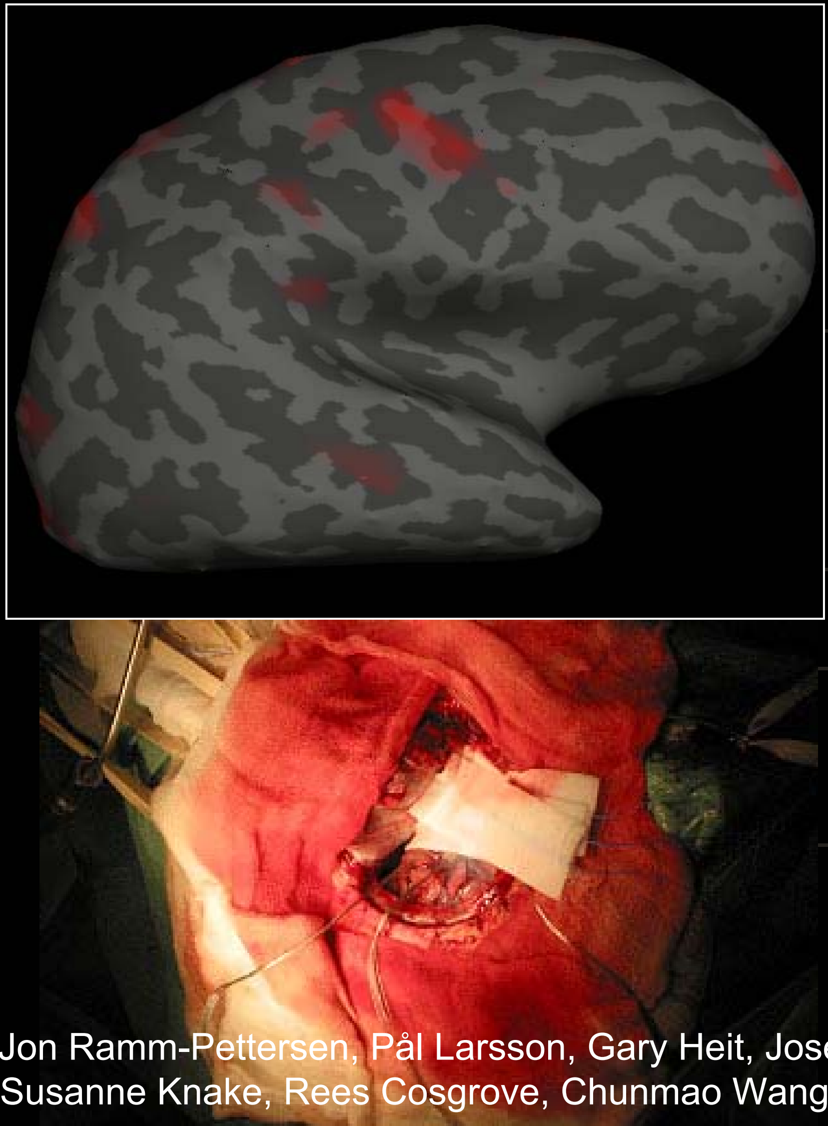


Origin and propagation of epileptiform spikes in humans studied at micro (laminar CSD/MUA) and macro (MEG) levels

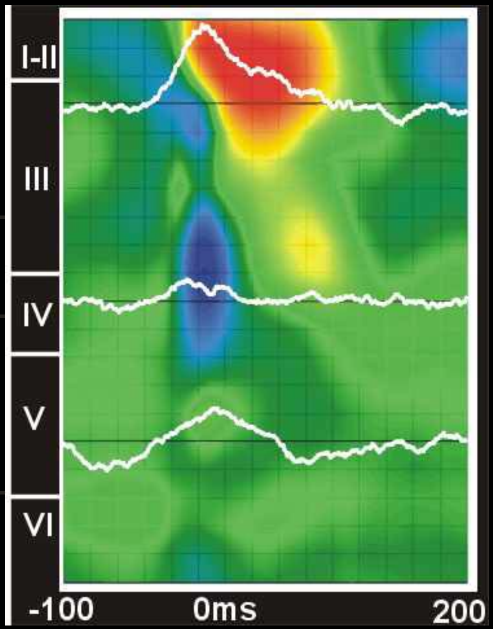
Transcortical propagation of an epileptic spike (MEG)

Neuronal circuitry of an epileptic spike within a cortical column at the focus of generation





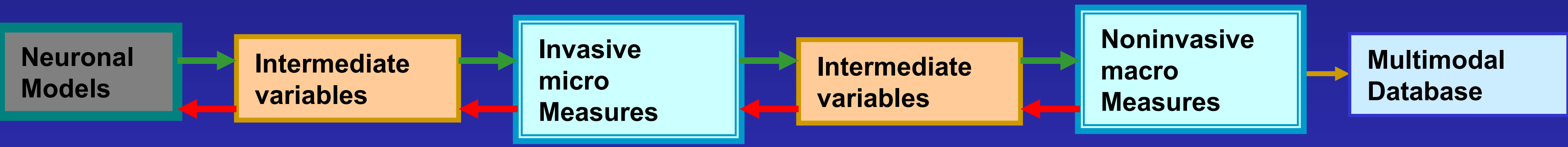
Neuronal circuitry of an epileptic spike distant from the generating site



Istvan Ulbert, Eric Halgren, Jon Ramm-Pettersen, Pål Larsson, Gary Heit, Joseph Madsen, Donald Schomer, Andrew Cole, Susanne Knake, Rees Cosgrove, Chunmao Wang, George Karmos

Fundamentals of an Approach

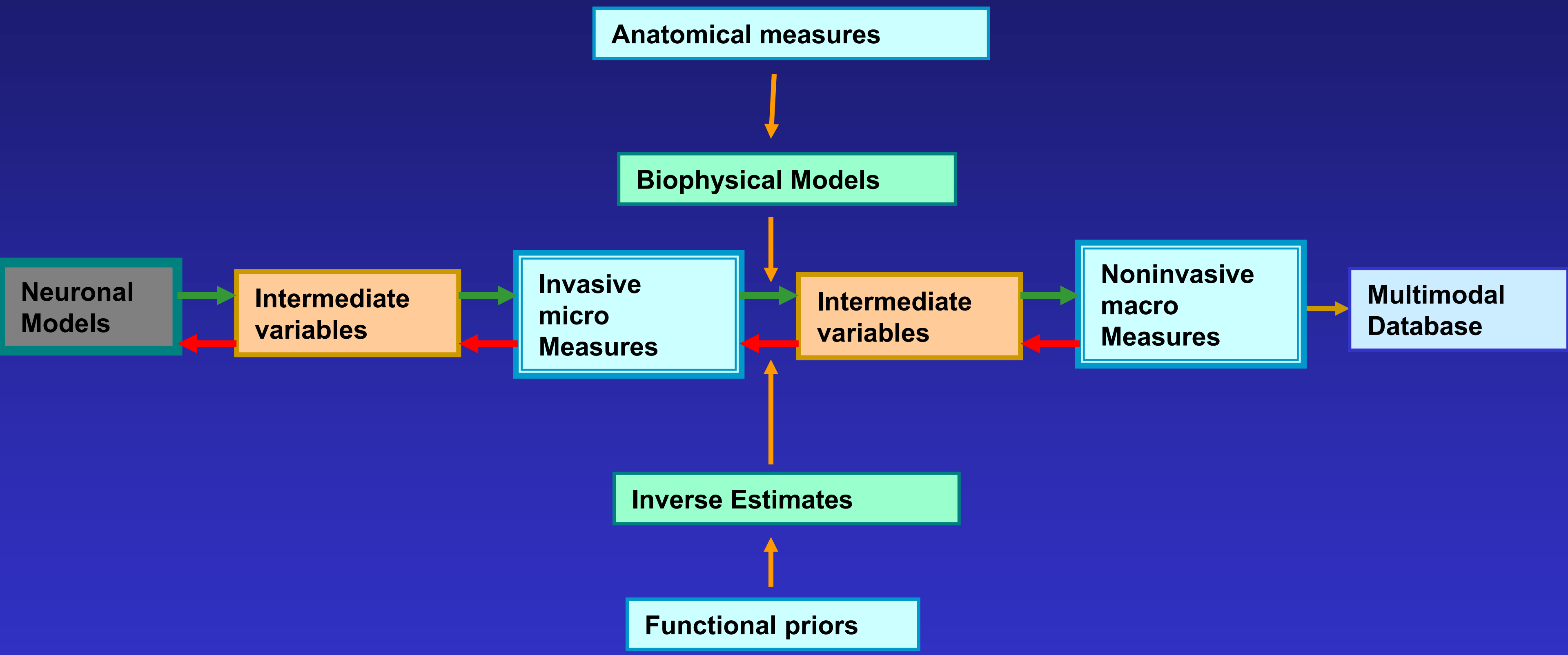
Multiresolution, Multispecies



Invasive micro-measures in animals and in human surgical cases are essential to establish relationships between measurements and physiological variables.

Fundamentals of An Approach

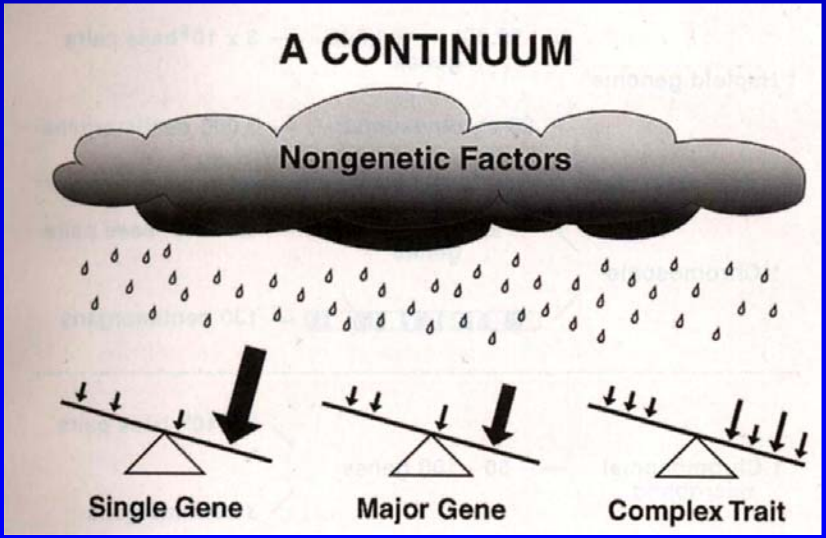
Multimodal



Obtain high spatial, temporal and physiological resolution by combining hemodynamic, structural, electromagnetic, and molecular probes

Discover the Genetic Basis of Behavioral Disease

Susceptibility to Illness Results from Different Combinations of Genetic, Epigenetic, & Environmental Factors



Beaudet et al. (2001) “The Metabolic & Molecular Bases of Inherited Disease” McGraw Hill

This is particularly true for complex diseases of the brain inherited in a non-mendelian fashion

Breiter & Gasic
A.A. Martinos

The Challenge:

Almost two decades of research attempting to link psychiatric disorders to susceptibility genes have not produced many replicating results.

Drug Dependent Behavior

↑

Traditional Approach: Bottoms Up

Genes

Diagnostic criteria based on BEHAVIOR group individuals with inherently different diseases.

We need better phenotypes to find the genes that increase the chance of addiction.

Breiter & Gasic
A.A. Martinos

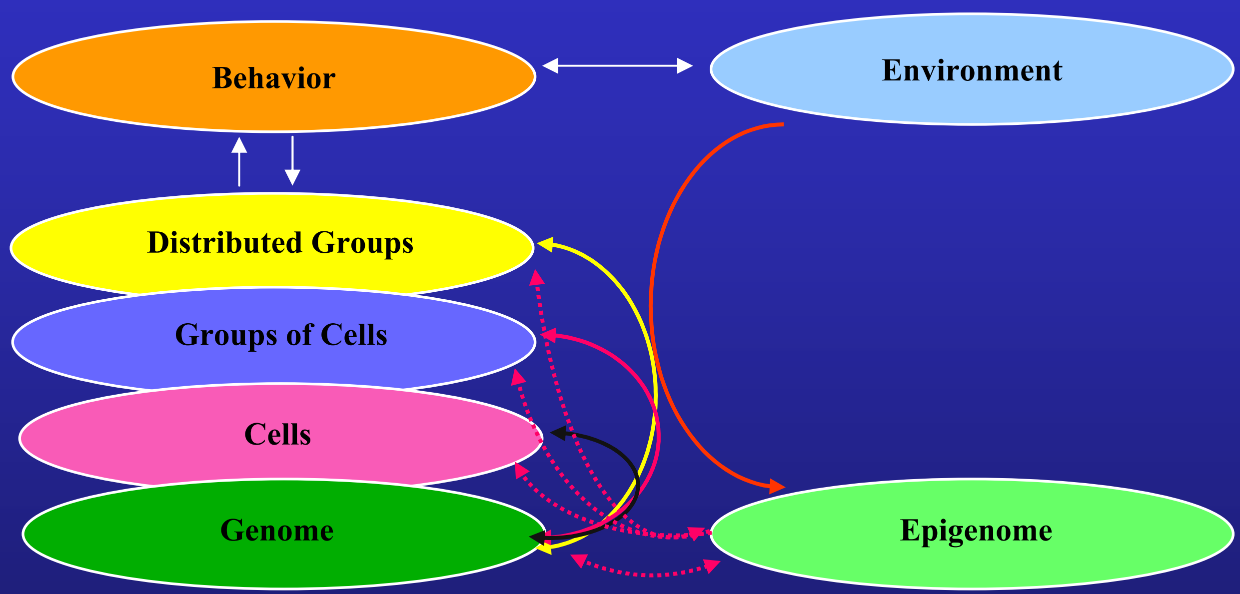
Strong Genetic Contribution to Addiction and Major Depression

Studies of mono- and di-zygotic twins give us a heritability estimate:

(a) of 0.5 - 0.6 for recurrent unipolar depression,

(b) of 0.7 - 0.8 (conservative) for nicotine, cocaine, and opiate dependence.

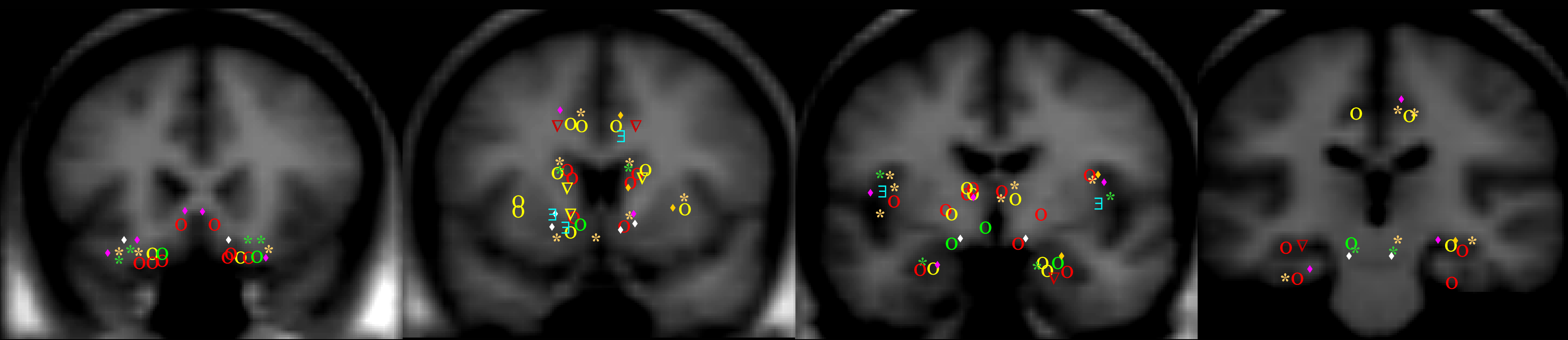
The Systems Biology approach to interaction of genome, epigenome, and environment.



Across this interface, the interaction of genome, epigenome, and environment determines the set of possible behaviors.

Breiter & Gasic
A.A. Martinos

Human Reward Circuity:
Overlapping Regions across Rewards



Monetary Reward

- O Guessing Paradigm
- O Performance Task
- O Prospect Theory Game

Appetative Reward

- * Passive Fluid/Chocolate
- * Passive Taste

Social-Aesthetic Reward

- ♦ Passive Viewing Beauty
- ♦ Passive Viewing Loved Face
- ♦ Passive Listening Music

Drug Reward

- ∇ Passive Inf Amphetamine
- ∇ Passive Inf Procaine

Probability Paradigms

- ∃ Cognitive Tasks Focussed On Probability Assessment

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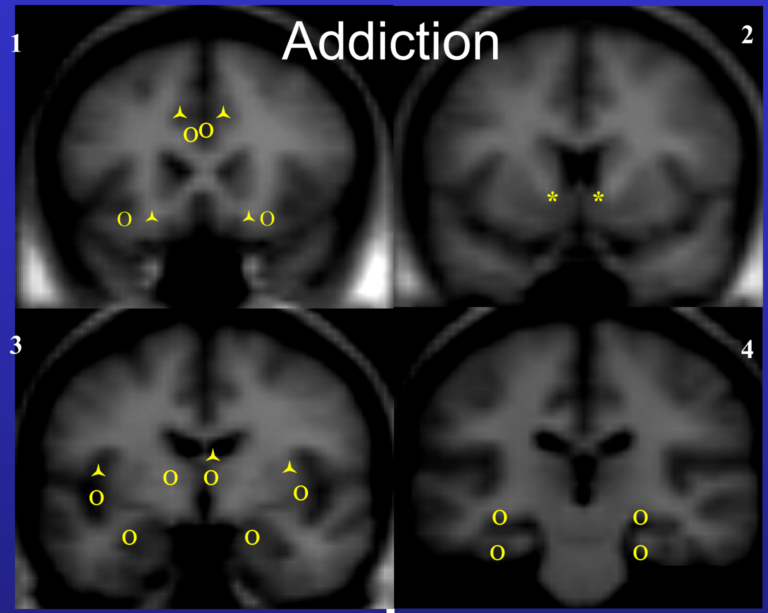
Endophenotype to genotype
Top Down Analysis



Set of Quantitative Traits

Multipoint Linkage Analysis

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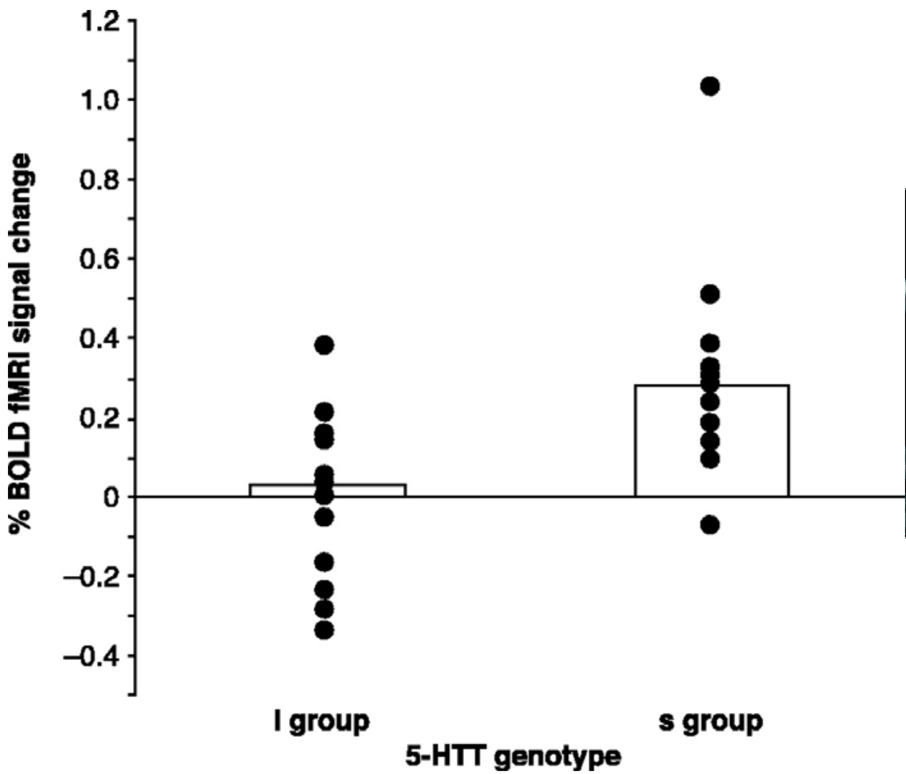
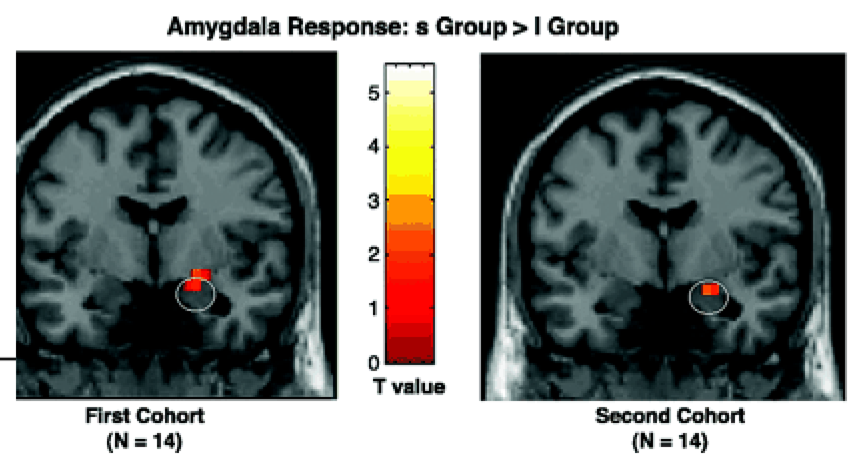
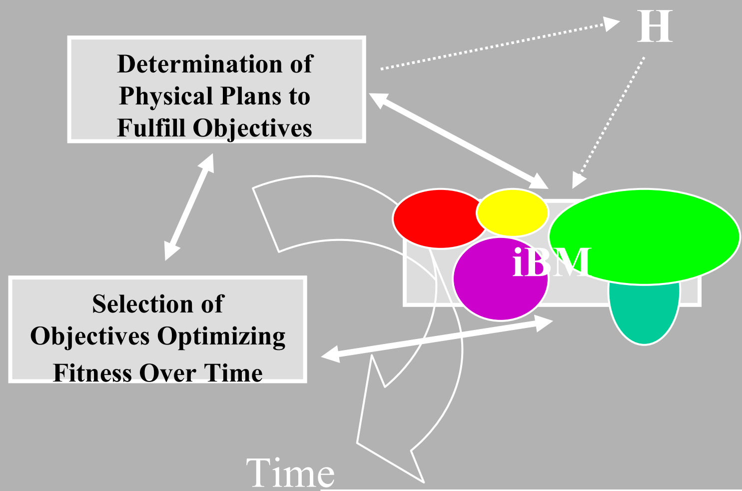
Individuals with a Serotonin Transporter Polymorphism Show an Increased Activation of the Amygdala and Increased Fear and Anxiety



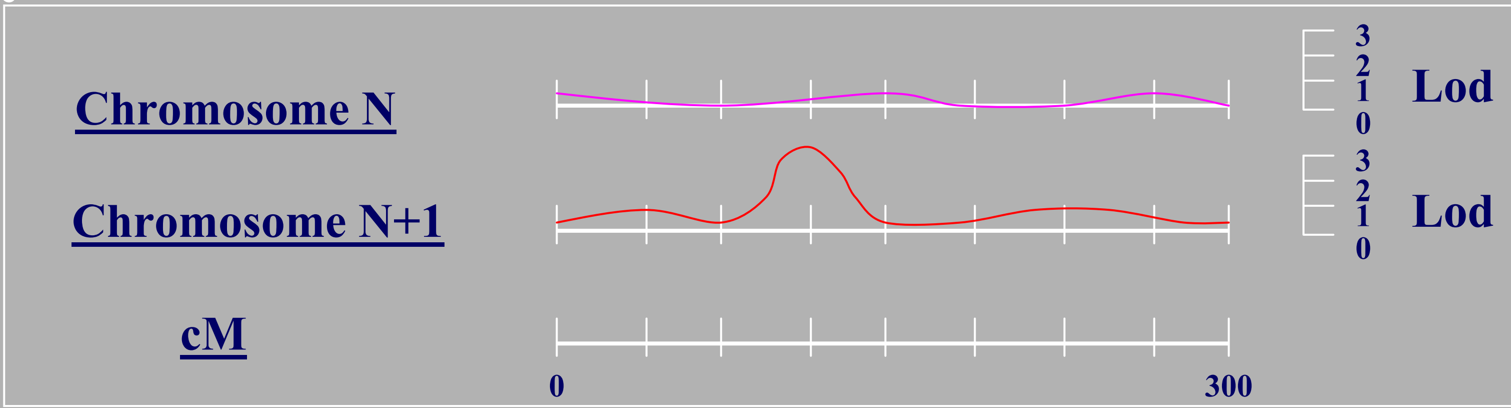


Hariri et al. Weinberger (2002) Science



Quantitative Traits from a Systems Biology Map

Expectancy				Outcomes								
Region		Cocaine	Monetary Reward	Region		Cocaine		Monetary Reward	Beauty		Pain	
						(1)	(2)		(+)	(-)	(+)	(-)
GOb	R			GOb	R	X	X	X^3	(X^2)		X^2	
	L	X^2	X^2		L	X	X	X^3				
NAc	R	X	X	NAc	R	X	X	X	X	(X)		X
	L	X	X		L	X				X		X
SLEA	R		X	SLEA	R	(X)	X	X	(X)		X	
	L				L	X				X		
Amygdala	R			Amygdala	R	(X)	X	X				
	L		X		L	X		X		(X)		(X)
VT	R			VT	R	X	X	X			X	
	L				L	X	X		(X)	X	X	



Multipoint Linkage Analysis

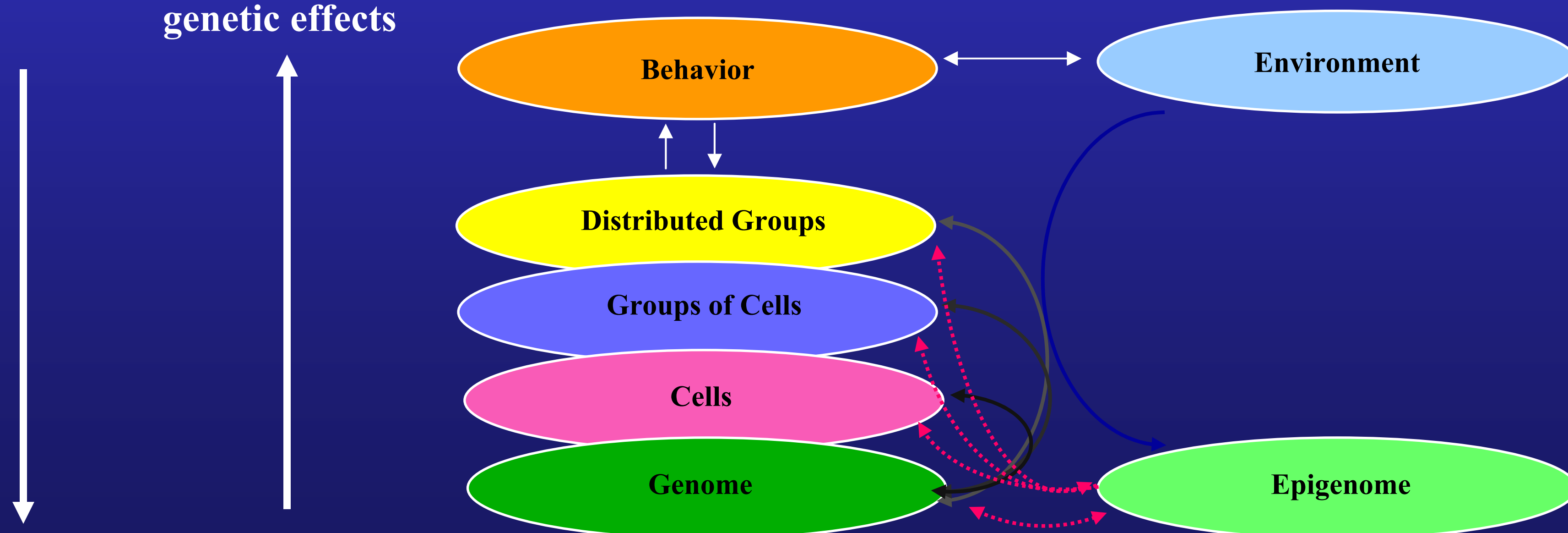
Example Chromosomal localization for Susceptibility to Addiction

Endophenotype	Chromosome	Position	Closest Marker	Lod Score
Quantitative MRI Trait #1	N	a - c	D N S_ _ _ _ _ _	“4”
	N + 3	g - h	D N+3 S _ _ _ _ _	“2”
Quantitative MRI Trait #2	N + 1	c - e	D N+1 S _ _ _ _ _	“5”
Quantitative MRI Trait #3	N + 2	d - f	D N+2 S _ _ _ _ _	“1”
Quantitative MRI Trait # M	N + M	x - y	D N+M S _ _ _ _ _	“x”

Breiter & Gasic, A.A.Martinos

Ultimately the confirmation of linkage findings is a bottom-up approach:

Top-down approach: systems biology to genes.
Bottom-up approach: genes to systems biology.



Breiter & Gasic
A. A. Martinos

The ethics of brain science

Open your mind

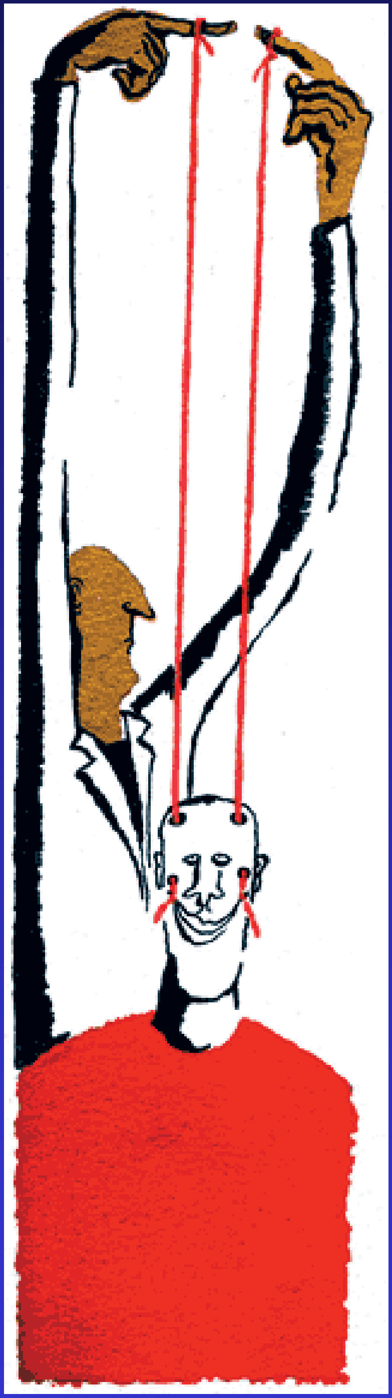
May 23rd 2002
From The Economist print edition

Genetics may yet threaten privacy, kill autonomy, make society homogeneous and gut the concept of human nature. But neuroscience could do all of these things first

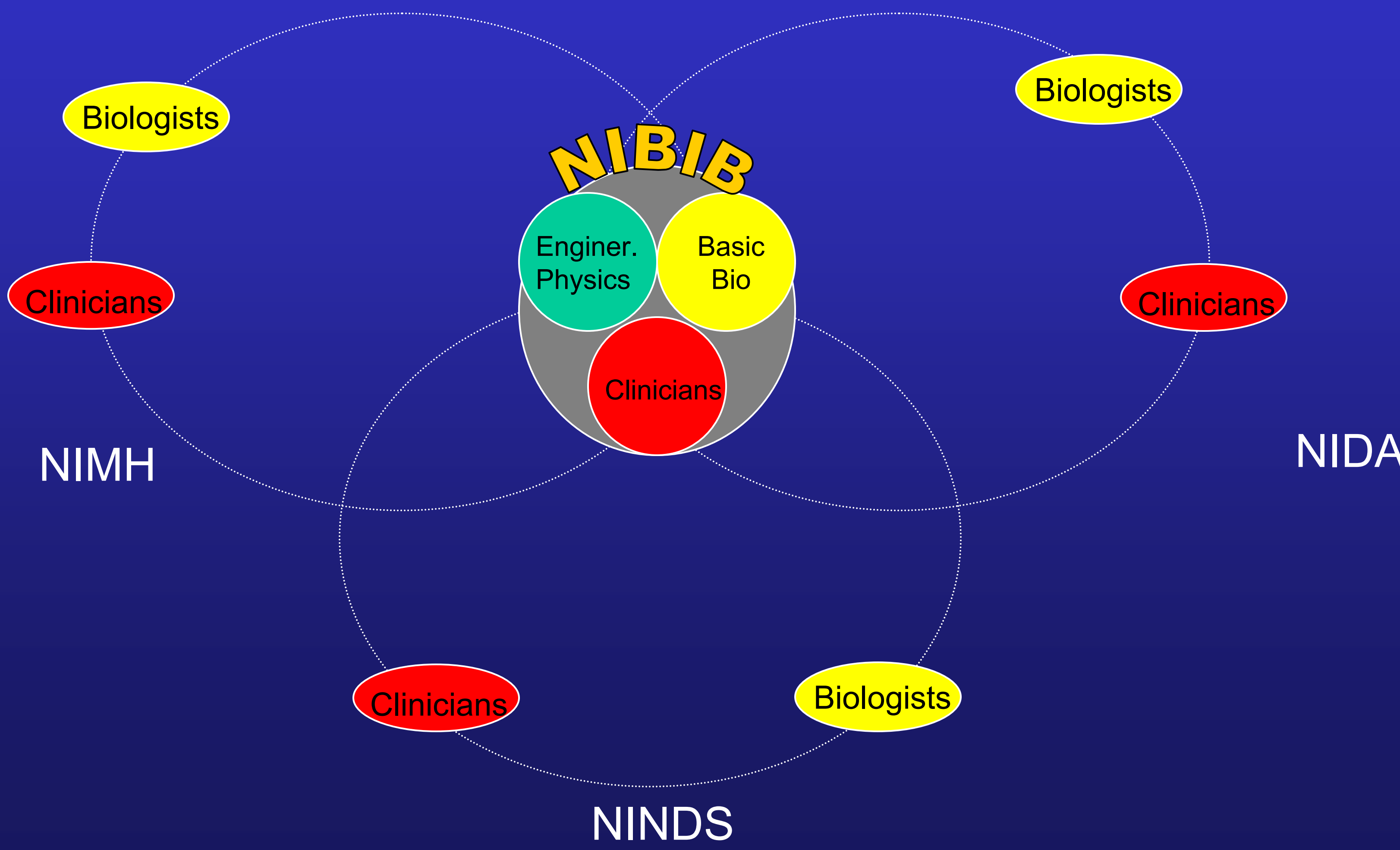
The Economist – May 23, 2002

“fMRI screening might, for example, become a foolproof method of lie detection—one that could catch out even “astute liars” who pretend to have impaired memories when put under pressure by an interrogator. Other personality traits, such as tendencies to aggression or risk-aversion, could also yield their secrets to fMRI's probing glance.”

“The really uncomfortable questions raised by brain science are those that go to the heart of what it is to be human. Or, more specifically, what philosophers and theologians have claimed is the heart of what it is to be human.”



NIBIB: Nuclear Model



Funding the Future of Functional Imaging